

PATENT COOPERATION TREATY

PCT

REC'D 23 DEC 2004

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

PCT



(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference JAB1730f-PCT | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416) | |
| International application No. PCT/EP 03/51042 | International filing date (day/month/year) 17.12.2003 | Priority date (day/month/year) 23.12.2002 |
| International Patent Classification (IPC) or both national classification and IPC C07D401/12 | | |
| Applicant JANSSEN PHARMACEUTICA N.V. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

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|---|--|
| Date of submission of the demand 01.06.2004 | Date of completion of this report 21.12.2004 |
| Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Stroeter, T Telephone No. +49 89 2399-8088  |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/51042**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-42 as originally filed

Claims, Numbers

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/51042**

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

| | | |
|-------------------------------|-------------|---------------|
| Novelty (N) | Yes: Claims | 1-17 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | 2, 9 |
| | No: Claims | 1, 3-8, 10-17 |
| Industrial applicability (IA) | Yes: Claims | 1-17 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/51042

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Prior art documents

Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

- D1: WO 02/32867 A (GLAXO GROUP LTD ; TRANQUILLINI MARIA ELVIRA (IT); MARAGNI PAOLO (IT);) 25 April 2002
- D2: WO 97/25322 A (PFIZER RES & DEV ; PFIZER LTD (GB); PFIZER (US); MACKENZIE ALEXANDER R) 17 July 1997
- D3: WO 02/062784 A (HOFFMANN LA ROCHE) 15 August 2002
- D4: US-B-6 262 0461 (MAGEE THOMAS VICTOR ET AL) 17 July 2001

2 Novelty (Article 33(2) PCT)

The present application is directed to substituted 1-(piperidin-4-yl)-4-(azetidin-3-yl)piperazine derivatives as neurokinine antagonists which are useful in the treatment of various diseases like anxiety, depression, schizophrenia, pain asthma, etc.

The structurally closest prior art compounds are the the piperidin-4-ylpiperazine compounds of D1 or D3 with the main structural difference being that the the presently claimed compounds have an azetidine group instead of substituent R5 of D1 (H, alkyl, COR6) or R^{1''} (e.g. cycloalkyl, pyridinyl) of D3. The azetidin-3-ylpiperazine compounds of D2 and D4 are even structurally more remote from the subject-matter of the present application.

Therefore present claim 1 and further claims 2-17 are novel.

3 Inventive step (Article 33(3) PCT)

These structural differences are, in principle, an inventive contribution to the problem of how to provide alternative neurokinine receptor antagonists in view of the compounds of D1 or D3 since the replacement of e.g. cycloalkyl with azetidine is nowhere indicated in the relevant prior art and it is well known in pharmaceutical chemistry that even small structural changes can lead to considerable changes in pharmacological activity, or to compounds with a completely different activity.

However, in view of this common knowledge it is not credible in view of the tested examples (wherein $m, n, p = 1$, $q = 0$ and $R^2 = \text{subst. phenyl}$) that all embodiments embraced by the scope of present claim 1 having the substituent R^2 and variables m, n, p and q with the definitions given in present claim 1 do exhibit neurokinine receptor antagonistic activity since there are **more structural differences between certain compounds of present claims 1, 3-8 and 10 and certain prepared and tested example compounds of the present application then there are structural differences between certain embodiments of the prior art D1 or D3 and certain present compounds claimed (e.g. D3, ex. 43: cyclopropyl instead of azetidine with $\text{Alk-Y-Alk-L} = \text{H}$, only structural difference: additional ring member N)**. The skilled man would therefore not have been able to predict if all compounds falling within the above definitions would actually be active as alleged.

Therefore claim 1 and consequently also claims 3-8 and 10-17 are not inventive. However, claims 2 and 9 are inventive due to the restricted meanings for $m, n, p (=1)$, $q (=0)$ and $R^2 (=Ar^2)$.

4 Industrial applicability (Article 33(4) PCT)

The subject-matter of the present set of claims 1 to 17 is in accordance with the requirements of Article 33(4) PCT.